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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,772	04/07/2006	Atsushi Miyawaki	P28025	6795

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EXAMINER	
LEE, JAE W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/538,772	MIYAWAKI ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/05/2006, 09/29/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In the amendment filed on 06/10/2005, Applicants have amended claims 3-7, 12-16, 19-21 and 23.

Claim(s) 1-23 is/are pending in this application.

Priority

A claim of priority to applications, PCT/JP03/15790, filed on 12/10/2003, and JAPAN 2002-357768, filed on 12/10/2002, is acknowledged.

Election

Applicant's election with traverse of Group III, Claims 21-23 with calmodulin, skMLCKp, and nucleus-localized sequence, in the response filed on 05/30/07, is acknowledged.

Applicants traverse on the basis that according to PCT rule Annex B, "[u]nity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims." Applicants further argue that *dependent* claims cannot be considered for unity of invention purposes.

Applicant's arguments are not deemed persuasive because as previously described, the unity of invention was properly considered "in relation to the independent" claim, i.e., claim 1. The prior art reference of Gautier et al. was discussed

only in relation to claim 1 that said reference teaches the limitations of claim 1 and that the shared technical feature of the groups is not a "special technical feature," hence the unity of invention between the groups does not exist (please see pg. 4 of previous restriction requirement).

Claim(s) 1-20 is/are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim(s) 21-23 is/are objected to because of the following informalities:

Claims 21-23 are objected to because they depend from a non-elected claim, i.e., claim 1.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is confusing in the recitation of the phrase, "so as to change the three-dimensional structure of the indicator or the expression vector of claim 22." It is unclear as to how "the expression vector of claim 22" is changed. It is suggested that applicants clarify the meaning of the noted phrase.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-23 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a genus of (1) nucleic acids encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; (2) an expression vector containing any nucleic

acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; and (3) a transformant having any nucleic acid, said nucleic acid encoding any fluorescent indicator, said fluorescent indicator formed by binding any fluorescent molecular component having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator or the expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification discloses only two representative species on pg. 28 of the specification, pRSET$_B$/W-cameleon obtained using primers, SEQ ID NOs: 40 and 41,

and pRSET$_B$/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector pRSET$_B$/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90). However, these two disclosed species fail to provide adequate written description for a genus of to a genus of (1) nucleic acids encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; (2) an expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; and (3) a transformant having any nucleic acid, said nucleic acid encoding any fluorescent indicator, said fluorescent indicator formed by binding any fluorescent molecular component having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator or the expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator.

In this case, the specification fails to describe any identification of structural characteristics or properties of a genus of nucleic acids encoding any fluorescent indicator, and how such structures have biologically relevant functions, i.e., homo-FRET or the ability to fluorescence when an analytical substance binds or reacts. It is noted by the Examiner that naturally occurring amino acids, i.e., phenylalanine, tyrosine, and tryptophan, are capable of fluorescence. Taken together, the genus of nucleic acids that encode any fluorescent indicator encompasses widely variant species, having essentially any structure. Please refer to the M.P.E.P. section 2163 [R-5] under II, A, 3, (a), (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus.

Given the lack of additional representative species of a genus of (1) nucleic acids encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; (2) an expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; and (3) a transformant having any nucleic acid, said nucleic acid encoding any fluorescent indicator, said fluorescent indicator formed by binding any fluorescent molecular component having substantially identical fluorescent properties to the N- and C-terminal

sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator or the expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator, as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for two vectors as disclosed on pg. 28 of the specification, $pRSET_B$/W-cameleon obtained using primers, SEQ ID NOs: 40 and 41, and $pRSET_B$/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector $pRSET_B$/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90), does not reasonably provide enablement for (1) nucleic acids encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target

sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; (2) an expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; and (3) a transformant having any nucleic acid, said nucleic acid encoding any fluorescent indicator, said fluorescent indicator formed by binding any fluorescent molecular component having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator or the expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

Claims 21-23 are so broad as to encompass any nucleic acid encoding the fluorescent indicator. However, the specification discloses only two vectors on pg. 28 of the specification, wherein Applicants disclose $pRSET_B$/W-cameleon obtained using primers, SEQ ID NOs: 40 and 41, and $pRSET_B$/W-SCAT obtained using primers, SEQ ID NOs: 42-45, with the template vector $pRSET_B$/Venus as disclosed in the reference of Nagai et al. (Nature Biotechnology, 2002, Vol. 20, pg. 97-90).

With regard to the use of all nucleic acids encoding any protein as a fluorescent indicator, it is noted by the Examiner that not all structurally different nucleic acids would be able to encode a fluorescent indicator that is capable of undergoing fluorescence at specific wavelengths, thereby generating different colors, i.e., yellow, green or red.

Therefore, the disclosure of a single example on pg. 28 of the specification in the reference of Nagai et al. does not commensurate with the breadth of claimed methods encompassing the use of all possible nucleic acids.

The claims rejected under this section of U.S.C. 112, first paragraph, do not place any structural limits on the "nucleic acid," or the encoded "fluorescent indicator." Since the amino acid sequence of a peptide determines its structural and functional properties, predictability of which peptides can be used while obtaining the desired function requires a knowledge of and guidance with regard to which amino acids in the peptide's sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the peptide's structure relates to its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different peptides/proteins.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any nucleic acid encoding any fluorescent indicator because the specification does not establish: (A) regions of the nucleic acid structure which may be modified without affecting the desired biological function, i.e., homo-FRET or the ability to fluorescence when an analytical substance binds or reacts; (B) the general tolerance of nucleic acids to modification and extent of such tolerance without affecting said desired biological functions; (D) a rational and predictable scheme for modifying any nucleic acid residue with an expectation of obtaining the desired activity/utility; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Because of this lack of guidance, and the fact that the relationship between the polypeptide sequence of a protein and its activity/function is not well understood and unpredictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to make and use the claimed nucleic acids.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any nucleic acid having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily,

and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 21-23 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nagai et al. (Circularly permuted green fluorescent proteins engineered to sense Ca^{2+}, PNAS, March 13, 2001, Vol. 98, No. 6, pg. 3197-3202).

The instant claims are drawn to (1) nucleic acids encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; (2) an expression vector containing any nucleic acid encoding

any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator; and (3) a transformant having any nucleic acid, said nucleic acid encoding any fluorescent indicator, said fluorescent indicator formed by binding any fluorescent molecular component having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator or the expression vector containing any nucleic acid encoding any fluorescent indicator formed by binding any fluorescent molecular components having substantially identical fluorescent properties to the N- and C-terminal sides of a target sequence, to which an analytical substance binds or reacts, so as to change the three-dimensional structure of the indicator.

The reference of Nagai et al. specifically teaches a fluorescent indicator, which is a circularly permutated EYFP (cpEYFP) having mutations at residues F46L, F64L, M153T, V163A, and S175G encoded by a nucleic acid sequence, wherein said cpEYFP is circularly permutated in such a way that the N-terminal end of the cpEYFP's fragment consisting of residues 1-144 is fused to the C-terminal end of the cpEYFP's fragment consisting of residues 145-238, wherein a linker, GlyGlySerGlyGly, is inserted in between said cpEYFP fragments (see Figure 1 and pg. 3197 under "Gene Construction"). The reference further discloses that the N-terminal of said cpEYFP was fused to M13, a 26-residue peptide derived from the calmodulin (CaM)-binding region of

the skeletal muscle myosin light-chain kinase, and the C-terminal of said cpEYFP was fused to CaM (see various chimeric proteins, that are circularly *per*mutated YFP and a *CaM*, named as "pericams" in Figure 1). The reference teaches that in the presence or absence of an analytical substance, i.e., Ca^{2+}, the spectral changes the "pericams" are detected by the changes in fluorescence excitation and emission spectra of the "pericams," which are "direct effects of the Ca2+-related structural change on the chromophore" (see the last sentence of 2nd paragraph, left column, on pg. 3200, and Figure 3). The reference of Nagai et al. also teaches the expression vector comprising said nucleic acid sequence, i.e. pcDNA3, (see right column, under "Gene Construction" on pg. 3197), and a transformant comprising the expression vector, i.e., E.coli [JM109(DE3)] (see left column, 2nd paragraph of pg. 3198). Taken together, the teachings of Nagai et al. anticipates the limitations of claim 21-23. Therefore, the reference of Nagai et al. anticipates the Applicants' claimed inventions.

Claims 21-23 are rejected under 35 U.S.C. § 102(e) as being anticipated by Tsien et al. (Fluorescent protein sensors for detection of analytes, US Patent No. 5,998,204).

The reference of Tsien et al. teaches a fluorescent indicator encoded by an isolated nucleic acid sequence, wherein said indicator comprises a binding protein moiety, i.e., calmodulin, a donor fluorescent protein moiety covalently coupled to the binding protein moiety, i.e., M13, and an acceptor fluorescent protein moiety covalently coupled to the binding protein moiety, wherein in the presence of an analyte, Ca^{2+}, the

donor moiety and the acceptor moiety change position relative to each other when the analyte binds to the analyte-binding region, altering fluorescence resonance energy transfer between the donor moiety and the acceptor moiety when the donor moiety is excited (see Figures 1-6). The reference of Tsien et al. also teaches an expression vector and a transformant, both comprising said nucleic acid sequence. Therefore, the reference of Tsien et al. anticipates the Applicants' claimed inventions.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-23 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21 of U.S. Patent No. 5,998,204. Although the conflicting claims are not identical, they are not patentably distinct from

each other because both sets of claims are drawn to a nucleic acid sequence which encodes a fluorescent indicator with overlapping scope in claimed nucleic acid sequence's structure and function.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming a common subject matter, as follows: an isolated nucleic acid sequence which encodes a fluorescent indicator, the indicator comprising: a binding protein moiety having an analyte-binding region which binds an analyte and causes the indicator to change conformation upon exposure to the analyte; a donor fluorescent protein moiety covalently coupled to the binding protein moiety; and an acceptor fluorescent protein moiety covalently coupled to the binding protein moiety, wherein the donor moiety and the acceptor moiety change position relative to each other when the analyte binds to the analyte-binding region, altering fluorescence resonance energy transfer between the donor moiety and the acceptor moiety when the donor moiety is excited.

The claims 21-23 in the instant application are fully anticipated by the disclosure of U.S. Patent No. 5,998,204 which was granted to a common inventor, Atsushi Miyawaki, of the instant application. It is noted by the Examiner that the assignee of the instant applicant and the U.S. Patent No. 5,998,204 are different.

Furthermore, there is no apparent reason why applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Conclusion

Claims 21-23 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner: Jae W. Lee, Ph.D.

RICHARD HUTSON, PH.D.
PRIMARY EXAMINER